REMARKS

Claims 2-5 and 7 are pending in the present application and are rejected. Claim 7 is herein amended. Applicants' thank the Examiner for the courtesies extended in the telephone interview of December 3, 2008. Applicants' Statement of the Substance of the Interview is incorporated herein.

Applicants' Response to Claim Rejections under 35 U.S.C. §112

Claims 2-5 and 7 were rejected under 35 U.S.C. §112, first paragraph, as not complying with the written description requirement. This is a new matter rejection.

It is the position of the Office Action that claims 2-5 and 7 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, it is the position of the Office Action that the specification does not disclose or discuss the feature that "beads each include one of a plurality of beads-ID and ...each of said beads-ID recognizing address linkers is specific to one of the plurality of beads-ID." This feature requires that each type of address linker 3 is specific to each type of beads-ID. However, it appears that the Office Action is of the position that all of the beads-ID in the specification are the same. Specifically, the Office Action states that "The specification does not appear to suggest different beads-ID at any point in the 4 page specification." The Office Action also notes that in Figure 2, all of the beads are allegedly illustrated identically. Thus, the Office

Action appears to regard all beads as being of a single type, and also appears to regard all address linkers 3 and addressing probe proteins as being the same.

In response, Applicants respectfully submit that the specification as filed provides sufficient support for the claim feature of "beads each include one of a plurality of beads-ID and ...each of said beads-ID recognizing address linkers is specific to one of said plurality of beads-ID." Applicants respectfully submit that even if, *arguendo*, this feature is not described *in ipsis verbis* in the specification, this feature would have been clear to one having ordinary skill in the art upon reading the specification as a whole.

First, Applicants discuss the problems of beads-utilizing protocols in the specification from page 2, line 31 to page 3, line 13. As explained at page 3, lines 4-6, conventional beads "have a disadvantage that each bead cannot be identified, that is, which DNA is bonded to which bead cannot be known." In other words, in a conventional bead-utilizing protocol, all beads are the same. Therefore, if more than one type of probe DNA is used, after beads are randomly "pulled down" to a substrate, the result is an array of beads, with the probe DNA of each specific bead being unknown. As such, it is not possible to efficiently study what binds to the multiple probe DNAs. Therefore, in the conventional beads-utilizing protocol, unless an *in situ* sequencing is performed, it is not possible to use more than one type of target DNA. As such, a conventional beads-utilizing protocol uses a single type of bead and a single type of probe DNA to study which of a variety of unknown biopolymers bind to the probe DNA. Accordingly, while a conventional beads-utilizing protocol may be helpful for in-depth study of a single probe DNA, it is not useful for a broad screening study of multiple probe DNAs.

The specification also discusses developments in beads-utilizing protocols where colored beads are used. See page 3, lines 6-11. In such a case, however, "only few identifiable types" of beads can be used. As an example, a protocol using colored beads could include Red, Green and Blue beads, detectable by appropriate imaging equipment. In this case, different probe DNAs could be used, but only the same number as the number of bead colors—in other words, the probe DNA would be specific to one type (color) of bead. For example, Red beads could have probe DNA #1 fixed to them, Green beads could have probe DNA #2 fixed to them, and Blue beads could have probe DNA #3 fixed to them. One color of beads, *e.g.*, Red beads, could be screened for, and the DNA or protein that binds to probe DNA #1 could be easily studied.

However, if a probe DNA #4 was added and fixed to one of the existing bead types (*e.g.*, Red beads), it would create confusion and uncertainty, since some Red beads would have probe DNA #1 fixed to them, and some Red beads would have probe DNA #4 fixed to them. Therefore, if Red beads were screened for, it would not be possible to easily determine whether the target biopolymers were binding to probe DNA #1 or probe DNA #4. Since there are only a very limited number of colors that a bead can have, this technology is very limited. This is why the specification explains that this type of system has "only a few identifiable types" of beads. As such, a protocol which uses colored beads is useful for the screening of a small number of probe DNAs. Due to the limited number of distinguishable colors, a colored bead protocol is not useful for a broad screening study of many probe DNAs.

However, as briefly explained at page 3, lines 11-13, Applicants have removed this limitation on the number of types of beads used by relying on the "antigen-antibody reaction of

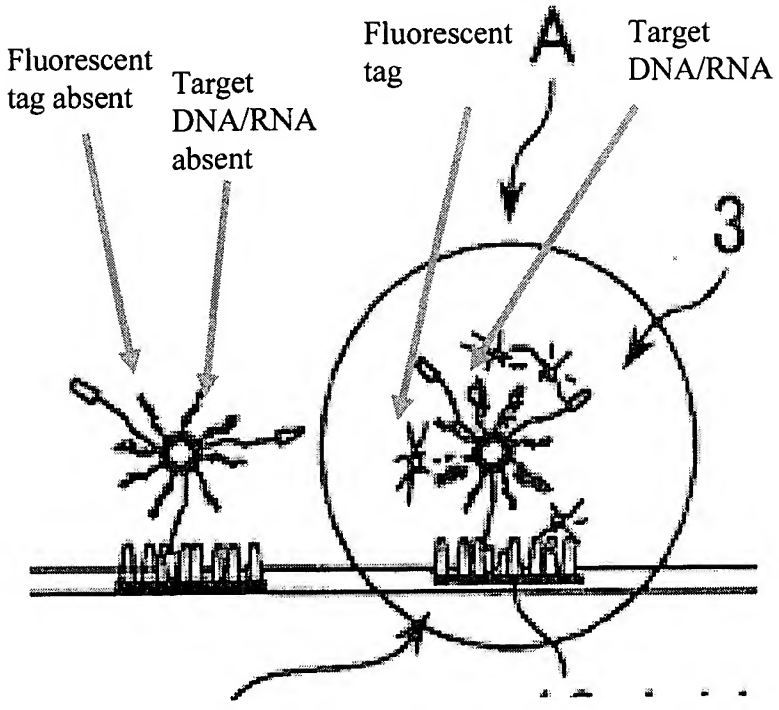
proteins location on the beads and the array." Since there are many types of antigen-antibody pairs (note the use of the plural form of the word "proteins" in line 13), the present invention allows for a system where, for example, a hundred different bead types could be utilized simultaneously. Such as system has great applicability for broad screening studies.

Applicants draw the Examiner's attention to the sentence at page 3, lines 23-25 of the specification, which states that "In addition to the above, address linker 3 (address-judging antigen or address-judging antibody) for recognizing specific beads number ID is fixed on the surface of beads 1." Applicants respectfully submit that this sentence clearly requires that one element is *specific for* another element. As noted above, in view of the background of conventional beads-utilizing protocols and colored beads-utilizing protocols, one having ordinary skill in the art would fully understand this sentence to mean that each address linker 3 is specific to a beads-ID. In other words, there are multiple types of beads in the system, and each type of bead shares the same unique address linker 3. This allows for unambiguous study of many probe DNAs. Due to the recited specificity, a user will know the ID of each bead after it is "pulled down" to the substrate. In other words, the recited specificity makes it such that beads are not randomly "pulled down" to the substrate, but rather, they are "pulled down" with specificity. Since the user would keep track of which probe DNA is bound to which bead ID, the user would then know the probe DNA at each location after the beads are "pulled down" to the substrate with specificity.

Additionally, Applicants note the Office Action's comment that "The specification does not appear to suggest different beads-ID at any point in the 4 page specification." Page 3, lines 9-

10. Thus, the Office Action interprets the specification such that all beads have the same beads-ID. Applicants' respectfully submit that this is an illogical position, since if all beads had the same beads-ID, there would be no need for "recognizing specific beads number ID." In other words, if all beads were identical, then there would be no need for an ID of beads. Similarly, if the invention only used a single antigen-antibody pair, there would be no need for address-judging antigens or address-judging antibodies.

In the telephone interview of December 3, 2008, Examiner Goldberg noted that all of the sites in Figure 2A and 2B appear to be the same, and thus, only one antigen-antibody pair is used. Applicants respectfully submit that that all sites in Figures 2A and 2B are not the same. For example, the third site from the left (circled and labeled "A") includes target DNA bound to probe DNA having a fluorescent tag, as illustrated below:



This part of Figure 2A is magnified in Figure 3. However, in Figure 2A, note that the circled site has target DNA/RNA and a fluorescent tag, while the non-circled sites do not have a target DNA/RNA and a fluorescent tag. Therefore, it cannot be said that each of the sites in Figure 2A are the same. Additionally, the site in Figure 2B corresponding to the circled site in Figure 2A is darkened, whereas the other sites are not. Although the specification does not discuss this darkening in detail, it would have been clear to one having ordinary skill in the art that this was a further illustration of the differences between the sites illustrated in Figure 2A.

Therefore, for at least the reasons discussed above, Applicants respectfully submit that the specification as filed fully supports all pending claims, and that no new matter has been added. Favorable reconsideration is respectfully requested.

Applicants' Response to Claim Rejections under 35 U.S.C. §103

Claims 2, 4, 5 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Balasubramanian et al. (WO 00/06770) in view of Chee et al. (U.S. Patent No. 6,858,394).

It is the position of the Office Action that Balasubramanian discloses the embodiments as claimed, with the exception of teaching spatially addressing the beads by an antigen/antibody reaction. The Office Action relies on Chee to provide this teaching, stating that Chee illustrates the addressability of specific substrates using analyte binding on a second substrate.

In the telephone interview of December 5, 2008, Applicants' representative and the Examiner discussed the prior art rejection. The Examiner appeared to agree that the primary

embodiment of Balasubramanian discloses an embodiment where all beads are from the same population. However, the Examiner maintains that other embodiments of Balasubramanian disclose multiple populations of beads. The Examiner mentioned that Balasubramanian discloses embodiments which utilize proteins to attach polynucleotides on a substrate. For example, at page 6, lines 13-15, it is stated that "the arrays may comprise protein molecules immobilized on a solid surface, the protein molecules being conjugated with or otherwise bound to a short polynucleotide may be interrogated, to address the array." First, Applicants respectfully submit that this passage refers exclusively to embodiments where a polynucleotide is directly fixed to a substrate, without the use of beads. Second, this passage does not state that the proteins are different from each other. In other words, this passage could simply be describing a situation where polynucleotides are bound to avidin to attach polynucleotides to biotinated substrate. Thus, Applicants respectfully submit that this passage does not disclose an embodiment where there are different populations of beads.

Also, the Examiner relies on page 8 of Balasubramanian, citing it extensively in the Office Action. In this discussion, Balasubramanian discusses "a nucleic acid molecule previously attached to a solid support" via streptavidin or avidin. Page 8, lines 1-6. Then, the solid support is brought into contact with a group of nucleic acids which include nucleic acids which are complementary to nucleic acids bound to the substrate, as well as nucleic acids which are not complementary to nucleic acids bound to the substrate. Balasubramanian discloses that this allows for "self-sorting" which can be used to "separate the desired polynucleotides from a heterogeneous sample of polynucleotides." Page 8, lines 10-11. This passage does not refer to

beads at all, and thus, Balasubramanian does not refer to self-sorting of target molecules to beads, or self-sorting of beads to a substrate. Accordingly, Applicants respectfully submit that the Office Action improperly mixes together the teachings of two separate embodiments discussed on page 8 of Balasubramanian (lines 1-11 vs. lines 22-28). Thus, Applicants respectfully submit that this passage does not disclose an embodiment where there are different populations of beads.

Additionally, Applicants discuss the passages of Balasubramanian at page 10, line 22 to page 11, line 2 and at page 11, lines 14-21. The passage at page 10, line 22 to page 11, line 2 discusses using a polynucleotide "incorporated onto a beaded support or reaction product" as a tag. This passage relates to an array where polynucleotides are attached in known positions. Synthesized polynucleotides are "specific for a particular product," and are allowed to hybridize with the known polynucleotides on the substrate. Such arrays could be re-used. Even if, *arguendo*, this passage refers to an embodiment where there are different populations of bead, such beads would only include the synthesized polynucleotide which potentially binds to the known polynucleotide on the array. Thus, Applicants respectfully submit that this passage is not related to the claimed invention.

Next, Applicants discuss the passage at page 11, lines 14-21. This passage discloses the use of "a second polynucleotide tag not involved in the hybridization to the array." Thus, it appears that the first polynucleotide would be used for spatial addressing of a bead and the second polynucleotide would be an unknown DNA which may be bound by other biopolymers. Even if, *arguendo*, this passage refers to an embodiment where there are different populations of

beads, this embodiment of Balasubramanian is significantly different from the claimed invention. This embodiment of Balasubramanian requires that the first nucleotide, which is used to spatially address the bead, be hybridized with the polynucleotide on the substrate before the second nucleotide is allowed to hybridize other biopolymers. If the second polynucleotide were permitted to hybridize with the other biopolymers before it is hybridized with the polynucleotide on the substrate, the other biopolymers could bind to the first polynucleotide, thus "blocking" the spatial addressing of the bead.

Therefore, Applicants herein amend the claims to further specify that the "capturing" step occurs after the "hybridizing" step. This amendment is supported at least by page 3, lines 28-36. Applicants respectfully submit that it would not have been obvious to modify the embodiment of Balasubramanian at page 11, lines 14-21 by doing the hybridizing prior to the bead attachment, since this could actually prevent the bead attachment. Furthermore, it would not have been obvious to modify the nucleotide attachment scheme of Balasubramanian by using an antigen/antibody pair. As discussed above, to perform addressing, it is necessary to prepare the same number of antigen/antibody combinations as the number of sites in the array. However, if the number of antigen/antibody combinations becomes large, it becomes difficult to utilize antigen/antibody interactions, due to crosstalk or dispersion of affinity of bonding strength. As such, generally, polynucleotides are used, as in Balasubramanian. Therefore, for at least the above reasons, Applicants respectfully submit that it would not have been obvious to combine the cited references in order to arrive at the embodiments as claimed. Favorable reconsideration is respectfully requested.

Claim 3 was rejected under 35 U.S.C. §103(a) as being unpatentable over Balasubramanian in view of Chee, and in further view of Collier et al. (U.S. Patent No. 5,985,548).

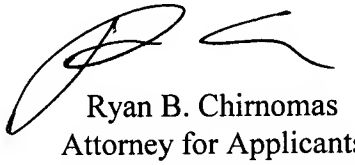
It is the position of the Office Action that the combination of Balasubramanian and Chee discloses the invention as claimed, with the exception of stirring beads. The Office Action relies on Collier to provide this teaching. In response, Applicants respectfully submit that claim 3 is patentable at least due to its dependency on claim 7, which Applicants submit is patentable for at least the reasons discussed above. Favorable reconsideration is respectfully requested.

Should the Examiner deem that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

WESTERMAN, HATTORI, DANIELS & ADRIAN, LLP



Ryan B. Chirnomas
Attorney for Applicants
Registration No. 56,527
Telephone: (202) 822-1100
Facsimile: (202) 822-1111

RBC/jw